AstraZeneca

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Date: APR 2 1 2005

Division of Dockets Management
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 2005D-0004
Response to FDA Call for Comments
Draft Guidance for Industry on Nonclinical Safety Evaluation of Drug Combinations

Dear Sir or Madam:

Reference is made to the January 26, 2005 Federal Register notice announcing the request for comments on the draft guidance for industry entitled "Nonclinical Safety Evaluation of Drug Combinations."

AstraZeneca has reviewed this draft guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Leonid Freytor, Associate Director, at (302) 886-2510.

Sincerely,

Barry Sickels, Executive Director
Regulatory Affairs
Telephone: (302) 886-5895
Fax: (302) 886-2822

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Enclosure

2005D-0004

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US Regulatory Affairs
AstraZeneca LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Docket Number 2005D-0004
AstraZeneca Response to FDA Call for Comments
Draft Guidance for Industry – "Nonclinical Safety Evaluation of Drug Combinations"

General Comments

- Comment 1

This is a comprehensive draft guidance that addresses fixed-dose combination products, co-packaged products, and adjunctive therapies. The guidance delineates three general categories of such drug combinations: 1) in which the 2 (or more) individual components are previously approved and marketed drugs (MDs), 2) in which one (or more) individual component is a previously approved and marketed drug (MD) and one (or more) is a new molecular entity (NME) and has not been previously approved or marketed, and 3) in which the 2 (or more) individual components are NMEs. The guidance discusses in detail the 3 general situations and identifies considerations and recommendations for each, taking into account current guidances and availability of information (MDs). The guidance represents a reasonable balance of risk vs. costs to develop new combination products. The primary concerns are (1) what is the drug ratio to be tested, (2) what are the endpoints to be evaluated in the bridging studies, and (3) the inconsistency between Sections III and IV in requests for safety pharmacology and/or animal models of efficacy studies as efficacy studies are outside the province of safety assessment. Thus, the focus should be on the safety pharmacology evaluations, not animal models for efficacy for safety assessment.

Draft Guidance for Industry – "Nonclinical Safety Evaluation of Drug Combinations"		
Section	**Page or Line Number**	**Comment or proposed replacement text**
Section II.A Safety Considerations	Lines 55-104	This section lists (1-9) a series of specific considerations to be taken into account for evaluation of the safety of drug combinations. It would be helpful to provide one or more specific examples to illustrate these considerations.
Section II.B Nonclinical Study Recommendations	Lines 125-128	"FDA recommends that combination studies include an assessment of several dose levels of the combination and a high dose of each drug alone." It is suggested that the text be changed to "Where appropriate, FDA recommends..." as it could be acceptable to do the combination only at a high dose of each where scientifically justified.
Section II.A, III.A, IV. A	Lines 122-125, lines 201-206, lines	"FDA recommends that the sponsor conduct a bridging study of up to 90 days with the combination..." It is suggested that the text be changed to "conduct a bridging study of a scientifically appropriate duration".

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Section	**Page or Line Number**	**Comment or proposed replacement text**
	254-257	As indicated in the general comments, the following statement is of concern. "For combinations, FDA recommends that the drugs be at ratios that are relevant to the intended clinical use." In the case of an NME/MD or NME/NME, it is likely that the clinical ratio will not be known at the time the preclinical studies are being planned. Thus, it would be a 'best guess' on the part of the preclinical team to try to accommodate this request. It would be helpful to provide clarification on how this could be achieved. There is also the question of whether the guidance is referring to ratio based upon exposure or dose, especially if a species cannot be identified that exhibit similar PK/ADME profiles for each of the components of the combination. Additionally, as at least one of the components of the combination is an NME that may not have been tested in humans at the time the studies are designed and conducted, human exposure could only be estimated using animal data and PK modelling programs. This concern is coupled to references made earlier in the document (Section II.B Nonclinical Study Recommendations (lines 125-128) regarding "Sponsors are urged to select the doses of each drug used in the combination to allow for additive or synergistic effects without unacceptable toxicity in the high-dose group." What would the agency interpret as "additive or synergistic" toxicities? Does this mean the same observations but at lower doses? Do both components have to be ramped up to demonstrate their respective expected toxicities, or is it sufficient to demonstrate only that the lowest NOEL or the most serious observation of the most toxic component repeats? Clarification by example or more substantive comments would be helpful. (This comment is also applicable to section IV.A, lines 263-266.)
Section III.B Reproductive and Developmental Toxicity	Lines 218-221	It is suggested to change the text of the FDA recommendation to read: "Embryofetal developmental studies of the combination should be conducted unless the marketed drug substance is already known to have significant risk for developmental toxicity or if the NME has been determined to have significant risk for developmental toxicity during the standard battery of nonclinical studies."
Section III.C, Section IV. B, see also general comment 1 (concern 3.)	Lines 225-228, lines 277-280.	This section explicitly requests that the efficacy of a proposed drug combination be demonstrated in an 'appropriate' animal model. The stated purpose of the requested evaluation is to determine whether one of the components of the combination alters the efficacy of one of the other components. Not stated explicitly, this section alludes to the possibility of negative pharmacokinetic of pharmacodynamic interactions. This section is the first (to this reviewer's knowledge)

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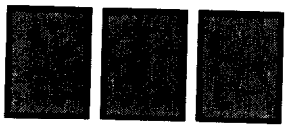
		of its kind (in a regulatory document) to specifically request nonclinical efficacy studies in a pathophysiological animal model of a human therapeutic condition, and as such breaks new regulatory ground. This reviewer notes that required animal safety studies are conducted in normal healthy young adults, and that recently requested juvenile animal safety studies are conducted using normal neonatal and juvenile animals. This section represents a new request to investigate the effects of drug combinations in pathophysiologic animal models of human disease for safety assessment, and (potentially) establishes a new nonclinical safety assessment paradigm and should be approached with great caution. This reviewer is unaware of any reliable data establishing the reliability of nonclinical pathophysiological models of human diseases to predict human safety issues. Indeed, the high rate of failure of new drugs in clinical development for insufficient/nonexistent clinical efficacy questions in the mind of this reviewer the wisdom of this section. This Reviewer suggests that this section be deleted, and that the broader issue of the role of pathophysiological animal models in nonclinical safety assessment be considered separately. The intent of this section, to detect a negative pharmacodynamic interaction could be addressed by a safety pharmacology evaluation of the combination (see section IV.C. lines 282-288).
Section IV.B Animal Models of Efficacy	Lines 275-289	See previous comments on section III.C above. This section appears to be redundant with section IV.C (lines 282-288).
Figure B	Lines 382-417	The figure does not reflect details of Section III; thus, impact of results of specific study types on decision-making is unclear.
Figure C	Lines 418-428	The figure does not reflect details requested in Section IV; thus, impact of results of specific study types on decision-making is unclear.



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